

## The Evidence Mounts Against Use of Pure Oxygen in Newborn Resuscitation

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The hardest exposures to indict as health hazards are common ones. Few will worry too much if an obscure dietary practice or a chemical found in only a handful of water supplies is implicated in disease, but the sometimes justified charge that epidemiologists are the “Chicken Littles” of biomedicine—repeatedly telling us that the sky is falling—usually emerges when the phenomenon labeled hazardous is familiar, routine, and ordinary. Such was the fate of smoking, whose risks took decades to become accepted, and it took quite some time too before the pediatric community as a whole was convinced that aspirin was a real cause of Reyes syndrome. The same can be said of oxygen, used for generations by physicians for a wide variety of therapeutic purposes. Anyone who doubts that oxygen is a popular element with the lay public should visit the oxygen bars now installed in many of our airports and shopping malls.

In this issue of *The Journal*, the analysis of Spector et al<sup>1</sup> of the venerable data of the National Collaborative Perinatal Project (NCP) describes a slightly higher risk of cancer in children exposed to >3 minutes of oxygen in the delivery room than in children without oxygen exposure. From the perspective of the individual, the excess risk is quite small. The NCP data suggest that a population of 10,000 unexposed children will have about 6 cancers by the age of 5, whereas 10,000 children exposed to >3 minutes of O<sub>2</sub> in the delivery room might experience 17 or 18 cases. The overwhelming majority of exposed children will not have cancer, which is the usual scenario when common exposures are implicated in disease, and the reason for popular skepticism. Everyone knows someone who is exposed to the risk, and it is overwhelmingly likely that the person you know will not have the disease in question. For example, 90% to 95% of smokers are never diagnosed with lung cancer.

From a public health perspective, of course, the numbers look different. Of the 48 cancers in the study, I calculated that 7, or nearly 15% of the total, might have been prevented if oxygen had not been used in resuscitation. To my knowledge, we have no other means available to remove about 1 in 7 cancers from the childhood population.

By now readers should be saying, “Stop! How do we know that this purported relationship between oxygen and cancer isn't spurious?” The short answer is, of course, that we don't. Absolute assurance is never available from relationships that emerge from observational research, but at the same time we cannot afford to ignore statistically significant observations made in large studies. The proper path between skepticism and faith in research is paved with careful scrutiny of the observation and its context. Applying that scrutiny in the discussion that follows, I use the term *oxygen* to indicate exposure to 3 or more minutes of oxygen, the exposure level where a cancer risk is indicated by the data, and follow some of the criteria that epidemiologists use in weighing observational evidence.

The study is one of the largest prospective studies of child health ever mounted, and the data on events in the delivery room were carefully collected and recorded years before most cancer diagnoses were established. Cancer in children is unlikely to be either missed or misclassified. Unfortunately, we cannot know exactly what concentration of oxygen these children were exposed to in the late 1950s and 1960s.

A range of variables were examined, and none seemed capable of explaining the association by confounding. Low Apgar score at 1 minute (but oddly, not at 5 minutes) was also associated with cancer risk, but less convincingly than oxygen. It is not unreasonable to suppose that if oxygen is a cancer risk, a low Apgar score would appear to be also, because the 2 phenomena necessarily cluster together, but the article does not tell us if controlling for oxygen eliminates the low Apgar association. But on the grounds of both biologic plausibility and strength of association, oxygen seems a more likely determinant of cancer

than birth depression. The relationship of oxygen to cancer—as judged by a hazard ratio of nearly 3—was of moderate strength, but with little evidence of a dose-response relationship, a criterion usually taken as favoring causality. Two other perinatal exposures have been assessed in relation to cancer in this cohort—maternal smoking in pregnancy and vitamin K administration in the newborn period—and both were exonerated, with nary a suggestion of elevated risk.<sup>2, 3</sup> These negative results lend a degree of specificity to the oxygen-cancer relationship. At a time when the consensus view is that the impending National Children's Study, with 100,000 births, will be too small to contribute to cancer epidemiology,<sup>4</sup> the NCPP, with about 50,000 births, is in fact doing so.

The data are consistent with a recent large Swedish case-control study (>500 childhood leukemia cases), which found a significant odds ratio of 2.6 for resuscitation with 100% oxygen with a facemask and bag after birth, which increased to 3.5 if manual ventilation lasted for 3 minutes or more.<sup>5</sup> In that study as well, low Apgar scores at 1 and 5 minutes were associated with leukemia, but not significantly so. The largest fraction of cancer cases in the study in this issue of the journal were leukemias.

Most readers will probably be interested in the biologic plausibility of the connection between oxygen exposure early in life and cancer later. The authors make 2 kinds of linkages. The first is to persistence of several indexes of oxidative stress in the serum of infants as late as a month after brief exposures to 100% oxygen in the delivery room.<sup>6</sup> The second is to the multiplicity of ways in which reactive oxygen species can damage DNA and otherwise contribute to the carcinogenic process, at several stages.<sup>7</sup> This kind of evidence has led to the hope that antioxidants might protect against cancer. Unfortunately the failure of antioxidant vitamins to prevent cancer (or heart disease for that matter) in randomized trials has proven a recurrent disappointment in epidemiology.<sup>8, 9, 10</sup>

Even if we did not worry about the carcinogenic potential of 100% oxygen (and the authors are admirably cautious in drawing conclusions), we would have good reasons to resuscitate most babies with room air. Increasingly we find that levels of PaO<sub>2</sub> in premature infants not previously considered hyperoxic may be dangerous to eyes,<sup>11</sup> lungs,<sup>12</sup> or brain.<sup>13</sup> Two recent meta-analyses of the relatively small number of trials comparing room air with 100% oxygen have concluded that room air resuscitation is superior, on several measures, including mortality, in asphyxiated babies.<sup>14, 15</sup> At the same time, one less-than-ideal follow-up of a randomized trial of room air versus 100% oxygen did not find significantly worse neurodevelopment in room air recipients at age 18 to 24 months.<sup>16</sup>

On balance, we do not have to be certain that the findings of Spector et al<sup>1</sup> are true. Added to the existing evidence, they tip the balance toward using room air, and not 100% oxygen, as the first line of treatment for most depressed newborns in the delivery room. Oxygen must be available in the delivery room, and there are some circumstances (eg, persistent fetal circulation, diaphragmatic hernia) where 100% oxygen should perhaps be first-line treatment. But even brief neonatal exposures to pure oxygen should no longer be considered familiar, routine, and ordinary.

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